

# Dalfampridine (Ampyra)

## An Aid to Walking in Patients with Multiple Sclerosis

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### INTRODUCTION

Multiple sclerosis (MS) is a neurological disorder that affects approximately 400,000 people in the U.S. and 2.5 million people worldwide, with women twice as likely to be affected as men.<sup>1-5</sup> This chronic disease stems from an autoimmune process characterized by axonal demyelination, which leads to inflammation within the central nervous system (CNS). MS is manifested by mental and physical symptoms characteristic of the illness.<sup>6,7</sup>

Risk factors for MS include ethnicity, genetics, and geographic location.<sup>4</sup> The initial clinical presentation of MS is usually seen between the ages of 20 and 40 years.<sup>2,3</sup> Patients typically present with weakness in the limbs, problems with gait and movement, sensory disturbances, fatigue, and visual difficulties. As the disease progresses, clinical symptoms begin to reveal cognitive deficits and increased neuropathic discrepancies.<sup>4,8</sup>

In addition to clinical data, diagnostics such as neuroimaging, evoked potentials, and cerebrospinal fluid (CSF) are performed in order to definitively identify

the presence of CNS lesions that may vary over time and space.<sup>2,7,9-11</sup> Discovering CNS lesions is important and can be accomplished by using evoked potentials through the stimulation of the eyes, ears, or peripheral nerve.<sup>2,7,9</sup> Magnetic resonance imaging (MRI) and CSF abnormalities are also assessed to confirm a diagnosis of MS.<sup>2,7</sup> Currently, the McDonald criteria constitute the most widely used diagnostic modality because they focus on clinical, laboratory, and radiologic data of MS lesions and their dissemination in time and space.<sup>12,13</sup>

There are various identifiable forms of illness:

- Most patients have relapsing-remitting MS. Initial symptoms, upon presentation, do not persist before the same or new symptoms appear.
- A number of patients have the secondary progressive form of MS, with symptoms progressively worsening; periods of remissions are partial or unrecognized.<sup>6,7</sup> These patients have disabling symptoms such as spasticity, exhaustion, visual disturbances, and difficulty urinating.<sup>6</sup>
- A smaller percentage of patients have primary progressive MS, characterized by advanced symptoms and disability from the onset of illness.
- A very small number of patients have progressive-relapsing MS.<sup>6,7</sup>

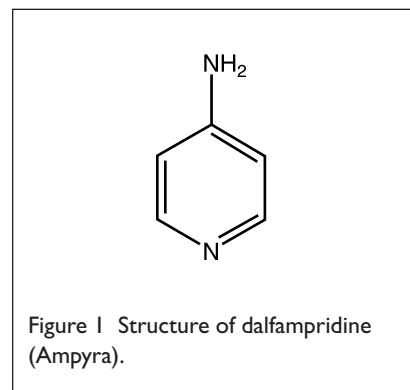
More than 90% of patients with MS report difficulty in walking.<sup>14</sup> Approximately half of all MS patients will require assistance with ambulation within 15 years of disease onset. Patient mobility is usually affected, to some extent, from the time of diagnosis, and it worsens progressively over time. Many patients present with fatigue, coordination difficulties,

post-exercise lethargy, and gait disturbances, all of which can compromise mobility.<sup>7,9,15</sup> Gait disturbances are particularly disabling and commonly result from one or more of the following: decreased muscle strength, spasms, or conduction and coordination defects.<sup>7,9</sup> Notably, about 50% of new patients experience loss of strength or decreased sensation in the extremities, and 30% of patients have spasticity that affects movement and daily living.<sup>7,10,15</sup>

MS is managed by agents such as corticosteroids and immunomodulators, which are used to treat symptoms, manage acute attacks, and slow disease progression. Other medications are also available to combat specific manifestations such as spasticity. Until earlier this year, physical therapy had been the only recommended course of action for those affected by gait disturbances. In January 2010, the FDA approved dalfampridine (Ampyra, Acorda) to help MS patients with walking. Dalfampridine was formerly known as fampridine.

### PHARMACOLOGY AND MECHANISM OF ACTION<sup>16-18</sup>

The exact therapeutic mechanism of dalfampridine is not clear. This potassium channel blocker enhances conduction in demyelinated axons of animals. In normal myelinated axons, concentrations



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of sodium channels are increased at the nodes of Ranvier, which cause action potentials to propagate. However, the area between the nodes is covered with myelin and contains a greater number of potassium channels (with many fewer sodium channels), which resist the generation of action potentials.

In axons that are demyelinated, action potential amplitude and duration are decreased because of the potassium channels that emerge on the axon plasma membranes. Dalfampridine increases the amplitude and duration of nerve conduction, resulting in enriched nerve conduction in demyelinated animal nerves.

Another potential mechanism of action includes the upsurge of skeletal muscle-twitch tension caused by the augmentation of synaptic transmission.

## PHARMACOKINETICS AND PHARMACODYNAMICS<sup>17,18</sup>

An oral medication, dalfampridine is quickly and completely absorbed in the gastrointestinal (GI) tract. It has a relative bioavailability of 96% and reaches peak concentration ( $C_{max}$ ) within three to four hours after administration. A slight and clinically insignificant increase in the  $C_{max}$  of dalfampridine is noted when it is taken with food; therefore, this drug may be taken without regard to meals.

Dalfampridine is 97% to 99% unbound to plasma proteins. Approximately 95.9% of a dalfampridine dose is excreted renally in the urine, and 0.5% is eliminated in the feces. As an extended-release formulation, it has an elimination half-life of 5.2 to 6.5 hours. Within 24 hours of administration, almost all of the drug and its metabolites are eliminated.

The enzyme cytochrome P450 2E1 (CYP 2E1) plays a major role in the conversion of dalfampridine to its 3-hydroxylated metabolites, most notably 3-hydroxy 4-aminopyridine and 3-hydroxy 4-aminopyridine sulfate, neither of which contributes pharmacologically. The sulfate conjugate has a half-life of 7.6 hours. The half-life of 3-hydroxy 4-aminopyridine has not been determined.

## CLINICAL EFFICACY<sup>17-20</sup>

The FDA's approval of dalfampridine was based on the results of one phase 2 and two phase 3 randomized, double-blind, placebo-controlled, parallel-group clinical trials (MS-F202 and MS-F203).

**Table 1 Ampyra: Summary of Key Information**

Brand name (generic name)	Ampyra (dalfampridine)
Pharmacological category	Potassium-channel blocker
Indication	To improve walking in multiple sclerosis patients
Dosage	10 mg by mouth every 12 hours; maximum daily dose, 20 mg
Adverse reactions (>2%)	Urinary tract infection, insomnia, dizziness, headache, nausea, asthenia, back pain, balance disorder, multiple sclerosis relapse, paresthesia, nasopharyngitis, constipation, dyspepsia, pharyngolaryngeal pain
Contraindications	History of seizure; moderate or severe renal impairment (creatinine clearance $\leq 50$ mL/minute)

Currently, three ongoing, long-term safety extension trials are also being conducted (MS-F202 Ext, MS-F203 Ext, and MS-F204 Ext).

### Goodman et al.<sup>19</sup> (MS-F202)

A phase 2 study was conducted to evaluate the safety and efficacy of three different strengths of dalfampridine (formerly fampridine) in 24 centers throughout the U.S. and Canada. Patients were randomly assigned to receive dalfampridine 10 mg ( $n = 52$ ), 15 mg ( $n = 50$ ), 20 mg ( $n = 57$ ), or placebo ( $n = 47$ ) twice daily for 14 weeks. Dose escalation occurred over two weeks for patients receiving higher doses of dalfampridine. After the 14-week trial period, patients were withdrawn from treatment, which was tapered over one week in the higher-dose groups. Patients were then observed for an additional two weeks.

Enrolled patients ranged from 18 to 70 years of age with MS of any type, and their average score of two timed 25-foot walk (T25FW) tests was 8 to 60 seconds. Patients were excluded if they experienced a recent relapse or medication change. In this trial, all four treatment groups were comparable in baseline patient demographics and clinical characteristics. Compliance with study medication was greater than 96% and comparable between groups.

The primary endpoint was the percentage of change from baseline in average T25FW. The secondary endpoint included change from baseline scores in the Lower Extremity Manual Muscle Test (LEMMT), the Ashworth Scale for

spasticity, the Subject Global Impression (SGI), the Clinical Global Impression (CGI), the 12-Item Multiple Sclerosis Walking Scale (MSWS-12), the Multiple Sclerosis Quality of Life Inventory (MSQLI), and the Multiple Sclerosis Functional Composite (MSFC) and its components, the Nine-Hole Peg Test (9-HPT) and Paced Auditory Serial Addition Test (PASAT). The investigators assessed the drug's safety by monitoring adverse events (AEs), vital signs, physical findings, laboratory test results, and electrocardiograms (ECGs).

In evaluating the primary endpoint, the researchers noted that the percentage of change from baseline in walking speed did not differ significantly between any of the dalfampridine groups or placebo patients. However, all three treated groups had larger increases in walking speed, and a greater proportion of treated patients experienced more than a 20% increase in walking speed (23.5% with dalfampridine 10 mg; 26% with 15 mg, 15.8% with 20 mg, and 12.8% with placebo).

During the trial, improvement in LEMMT scores was greater with dalfampridine 10 mg ( $P = 0.018$ ) and 15 mg ( $P = 0.003$ ), compared with placebo; however, this change did not apply to the 20-mg dose. No significant differences in any other assessed secondary measure were observed.

There was no significant difference in overall frequency of AEs in the dalfampridine 10-mg (87%) and placebo groups (81%). It is noteworthy that the most common AEs were falls, nausea, asthe-

nia, headache, fatigue, and insomnia. The dalfampridine 10-mg twice-daily patients and the placebo-treated groups differed most significantly in regard to falls (19% with dalfampridine vs. 11% with placebo, respectively) and asthenia (19% vs. 2%, respectively).

Patients who received higher doses (15 mg twice daily vs. 10 mg twice daily) experienced an increased risk of insomnia (20% vs. 10%, respectively) and dizziness (20% vs. 4%, respectively). All other AEs were similar between the dalfampridine and placebo groups. However, because of the variability of effects seen with patients taking dalfampridine 20 mg twice daily, no clear relationship between doses and AEs could be concluded. For example, falls were experienced by 19% of patients receiving 10 mg twice daily and by 20% of patients receiving 15 mg twice daily. Only 9% of patients receiving dalfampridine 20 mg twice daily experienced AEs such as falls.

One placebo patient discontinued treatment following a myocardial infarction (MI). None of the patients in the dalfampridine 10-mg group withdrew. One patient receiving dalfampridine 15 mg withdrew because of nausea and dizziness, and five patients in the dalfampridine 20-mg group discontinued therapy—two patients because of seizures and one patient each because of abnormal coordination, chest discomfort, headache, and complex CNS effects. No deaths were reported. Some patients had clinically significant changes in laboratory values, vital signs, or ECG findings, but there were no apparent trends within or between the treatment groups.

The results suggest that dalfampridine 10 mg twice daily had a more favorable benefit-to-risk profile compared with 15 or 20 mg twice daily. The researchers indicated that using a responder approach (analysis of walking speed) could demonstrate a clinically meaningful effect in patients with walking impairment caused by MS.

### Goodman et al.<sup>20</sup> (MS-F203)

The efficacy and safety of dalfampridine for improving ambulation in adult patients with MS were investigated further in a phase 3, multicenter trial conducted throughout the U.S. and Canada. During the study period, 300 patients were randomly assigned to receive ei-

ther dalfampridine 10 mg or placebo twice daily. After the 14-week treatment period, patients were observed for an additional four weeks. Enrolled patients were 18 to 70 years of age with more than a two-month history of MS of any type. The average T25FW test was 8 to 45 seconds.

Patients with a history of seizures and those with recent changes in their therapy for MS (drug or dosage) were excluded. Treatment groups were comparable in baseline patient demographics and clinical characteristics. Compliance with study medication was greater than 97% for both treatment groups.

The primary endpoint was response to treatment, which was defined as a faster walking speed on two T25FW tests on at least three of four visits, compared with the maximum speed for any of five baseline off-treatment visits. The test was performed twice at each visit, allowing a maximum of five minutes of rest between each test. The average of both scores was used in analysis. Missed assessments were assumed to fall within the off-treatment range. Patients were allowed to use assistance devices as long as they were used consistently for all visits.

Secondary endpoints included change from baseline in the Ashworth scores for spasticity and Lower Extremity Manual Muscle Test (LEMMT) scores. An average post-baseline value was assigned for any missing secondary values during the treatment period. Ashworth scores for spasticity and LEMMT scores were stratified by response. Safety was also assessed by monitoring AEs, vital signs, clinical laboratory measures, and ECGs.

Of the 300 patients enrolled in the trial, 35% of those receiving dalfampridine and 8% of those receiving placebo reached the primary efficacy endpoint. Higher proportions of patients receiving dalfampridine showed improvement in average change from baseline in MSWS-12 scores (–6.84) than did non-responders (0.05). This indicates a reduction in self-assessed ambulation disability in timed-walk responders.

The average changes from baseline in walking speed in dalfampridine-treated responders were 25.2% and 4.7% in the placebo group, and the increase in walking speed was maintained over the 14-week treatment period. The average change from baseline in walking speed in

dalfampridine-treated non-responders was 7.5%, which was significantly greater than the average change for the placebo group at the earliest double-blind period visit only.

Dalfampridine-treated responders and non-responders showed more improvement in average Ashworth scores compared with the placebo group, but the difference between the dalfampridine responders and placebo groups was not significant.

During the treatment period, average improvement in LEMMT scores for dalfampridine-treated responders was 0.18, compared with 0.04 for the placebo group. The dalfampridine-treated non-responders also experienced greater improvement in average LEMMT scores (0.11), compared with placebo subjects (0.046).

Rates of AEs were similar in all treatment groups. The most frequently reported AEs among all patients included falls, urinary tract infections, dizziness, insomnia, fatigue, and pain-related symptoms. One or more serious AEs were reported in 16 dalfampridine patients (7%); two of these AEs were considered to be potentially related to therapy (one case of severe anxiety in a patient with pre-existing anxiety and insomnia and one focal seizure in a patient). Eleven dalfampridine patients and none of the placebo patients discontinued therapy because of AEs. No patients died during the course of the study.

At the end of the trial, the clinicians received a summary questionnaire showing that they had correctly identified drug assignment for 38% of the dalfampridine patients and 33% of the placebo individuals. However, no significant unblinding was suspected.

### MS-F204<sup>17,18</sup>

The positive findings demonstrated by the MS-F203 study allowed for a second pivotal phase 3 trial of dalfampridine (MS-F204). In this multicenter trial, 239 patients throughout the U.S. and Canada were randomly assigned, in a 1:1 ratio, to one of two treatment groups for nine weeks. The timeline of the study specifically incorporated one week of screening, two weeks of placebo, nine weeks of double-blind treatment (dalfampridine 10 mg vs. placebo twice daily), and two weeks of follow-up (14 weeks total).

Patients had to be 18 to 70 years of age with a history of MS of any type and an average T25FW test of 8 to 45 seconds. Patients with a history of seizures or recent changes in their therapy for MS (medication or dosage) were excluded.

The primary endpoint was the response to treatment based on increased walking speeds (measured by two T25FW tests) on at least three or four visits during the treatment period compared with maximum speed during any other visits while they were off treatment. A secondary endpoint was improved leg strength, as measured by a change from baseline in Ashworth scores for spasticity and LEMMT scores among timed-walk responders and non-responders in both study groups. Using this secondary endpoint, researchers could analyze the participants' leg strength in correlation with the primary endpoint of walking speed.

The safety of dalfampridine was evaluated throughout the entire study period, and efficacy was evaluated over the nine weeks of double-blind treatment. Pharmacodynamic data were also collected in the final week in order to determine the effectiveness of treatment.

Of the 239 patients enrolled in the trial, 42.9% of those receiving dalfampridine and 9.3% of those receiving placebo reached the primary efficacy endpoint. Participants in the dalfampridine group also showed a significant increase in walking speed of at least 10%, 20%, or 30% from baseline values, compared with the placebo arm. A higher percentage of patients receiving dalfampridine also improved in average change from baseline MSWS-12 scores (-2.54) than those receiving placebo (0.83), indicating a significant reduction in self-assessed ambulation disability in timed-walk responders ( $P = 0.036$ ).

A greater average improvement of LEMMT scores was also observed during the treatment period in the dalfampridine responders compared with the placebo patients (0.145 vs. 0.042, respectively;  $P = 0.028$ ). As for dalfampridine non-responders, similar nonsignificant improvements in average LEMMT scores were observed in both study groups.

Participants also completed a Subject Global Impression (SGI), allowing for a

subjective analysis of each patient's perception of health status. Interestingly, this assessment demonstrated no significant difference between the treatment groups in their perception of events on their physical well-being (placebo, -0.04; fampridine, 0.09).

Treatment-related AEs were reported more often for dalfampridine than for placebo. A similar number of patients in each group discontinued treatment because of AEs. The most frequently reported AEs among all study participants included urinary tract infections (17.5% with dalfampridine vs. 8.4% with placebo, respectively), falls (11.7% vs. 16.8%), insomnia (10.0% vs. 1.7%), headache (9.2% vs. 0.8%), asthenia (8.3% vs. 4.2%), dizziness (8.3% vs. 0.8%), nausea (8.3% vs. 0.8%), and pain-related symptoms (5.8% vs. 1.7%). No deaths occurred during the study, but one or more serious AEs were reported in 2.5% of the dalfampridine group and in 4% of the placebo group.

In both phase 3 trials, participants were permitted to continue all previously prescribed medications for MS (i.e., immunomodulators) as long as they were stable with these agents for at least 60 days. Of all patients included in these trials, 63% were receiving concomitant immunomodulatory therapy; however, it was determined that the degree of improvement in walking ability was not related to these medications.

### ADVERSE DRUG REACTIONS<sup>17-19</sup>

The most common AEs reported with the use of dalfampridine include urinary tract infections, insomnia, dizziness, headache, nausea, asthenia, back pain, impaired balance, MS relapse, paresthesia, nasopharyngitis, constipation, dyspepsia, and pharyngeal pain. Dalfampridine has not been noted to prolong the corrected QT interval (QTc) or to have a clinically important effect on the duration of the QRS interval; however, a dose-dependent increase in the incidence of seizures has been observed in various clinical trials. Therefore, prescribers and patients should be judicious with drug dosage and administration.

### DRUG INTERACTIONS<sup>17,18</sup>

To date, no clinically significant drug interactions have been identified with the use of dalfampridine. However, patients

should be encouraged to inform their health care practitioners of all prescription, herbal, and over-the-counter medications they are taking.

### CONTRAINDICATIONS<sup>17,18</sup>

The use of dalfampridine is contraindicated in patients with a history of seizures and in those with moderate or severe renal impairment, defined as a creatinine clearance (CrCl) of 50 mL/minute or less.

### PRECAUTIONS AND WARNINGS<sup>17,18</sup>

The risk of seizures increases as the dose of dalfampridine increases. It is also suspected that drug plasma levels in patients with mild renal impairment (CrCl, 51–80 mL/minute) might be associated with an increased risk of seizures as well. Therefore, renal function and seizure risk must be assessed before dalfampridine therapy is begun. If seizures occur while the patient is taking dalfampridine, the drug should be discontinued and not re-initiated.

As a Pregnancy Category C drug, dalfampridine should not be taken with any other forms of 4-aminopyridine. Dalfampridine should be used with caution in nursing mothers because it is unknown whether it is excreted in human milk.

### DOSAGE AND ADMINISTRATION<sup>17,18</sup>

The maximum recommended dose of dalfampridine is 10 mg twice daily, taken with or without food. No additional benefits are observed with doses above this maximum. Each dose should be taken about 12 hours apart, and patients should be discouraged from taking double or extra doses if a dose is missed. Tablets should only be taken whole; they should not be divided, crushed, chewed, or dissolved.

Dalfampridine (Ampyra) is supplied as 10-mg film-coated, extended-release, white to off-white, oval tablets. The product should be stored at room temperature (25°C, or 77°F), with variations permitted between 15 and 30°C (59° to 86°F).

### COST<sup>21</sup>

According to the 2010 edition of *Red Book*, the average wholesale price of a bottle of 60 tablets is listed as \$1,267.39.



## CONCLUSION

During the course of MS, the majority of patients experience walking difficulties. Dalfampridine offers a novel therapeutic option for these patients, as demonstrated by the increases in walking speeds observed in various clinical trials. It is a safe and well-tolerated agent that may be used alone or in combination with other MS therapies.

P&T committees, as well as pharmacy benefit management (PBM) organizations, should consider the addition of dalfampridine to their formularies for MS patients with walking difficulties despite appropriate maintenance therapy. The cost of treatment may actually be considerably less than the overall long-term costs of MS because of the drug's potential to improve quality of life for many patients and to delay or prevent debilitating complications resulting from mobility problems.

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